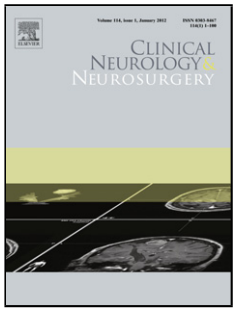

Title: Myelin Water Fraction Changes in Febrile Seizures

Authors: Krisztina Moldovan, Jerrold L. Boxerman, Jonathan O'Muircheartaigh, Doug Dean, Stephanie Eyerly-Webb, G. Rees Cosgrove, Frank Pucci, Sean C.L. Deoni, Heather S. Spader

PII: S0303-8467(18)30406-2
DOI: https://doi.org/10.1016/j.clineuro.2018.10.005
Reference: CLINEU 5191

To appear in: *Clinical Neurology and Neurosurgery*

Received date: 12-8-2018
Revised date: 27-9-2018
Accepted date: 7-10-2018

Please cite this article as: Moldovan K, Boxerman JL, O'Muircheartaigh J, Dean D, Eyerly-Webb S, Cosgrove GR, Pucci F, Deoni SCL, Spader HS, Myelin Water Fraction Changes in Febrile Seizures, *Clinical Neurology and Neurosurgery* (2018), https://doi.org/10.1016/j.clineuro.2018.10.005

Myelin Water Fraction Changes in Febrile Seizures

Running Title: Myelination patterns in febrile seizures

Krisztina Moldovan, M.D.[a*], Jerrold L. Boxerman, M.D., Ph.D.[b], Jonathan O'Muircheartaigh, Ph.D.[c], Doug Dean, Ph.D.[d], Stephanie Eyerly-Webb, Ph.D.[e], G. Rees Cosgrove, M.D.[f], Frank Pucci, M.D.[a], Sean C. L. Deoni, Ph.D.[g], Heather S. Spader, M.D.[h]

[a]Department of Neurosurgery, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA; kmoldov1@gmail.com

[b]Department of Diagnostic Imaging, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, USA; JBoxerman@lifespan.org

[c]Imaging and Biomedical Engineering Clinical Academic Group, King's College, London, UK; jonathanom@kcl.ac.uk

[d]Waisman Center, University of Wisconsin-Madison, 1500 Highland Ave, Madison, WI 53705, USA; douglas.c.dean.iii@gmail.com

[e]Office of Human Research, Memorial Healthcare System, 3501 Johnson Street, Hollywood, FL, 33021, USA; seyerlywebb@mhs.net

[f]Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Neurosciences Center, 60 Fenwood Road, 1st Floor, Boston, MA 02115, USA; rcosgrove2@bwh.harvard.edu

[g]Brown University Advanced Baby Imaging Lab, Memorial Hospital of Rhode Island, Department of Pediatrics, 111 Brewster Street, Pawtucket, RI 02860, USA; sdeoni@mac.com

[h]Division of Pediatric Neurosurgery, Joe DiMaggio Children's Hospital, 1150 N 35th Ave, Hollywood, FL 33021, USA; hspader@mhs.net

*Corresponding author. Phone: 301-908-5046 Email: kmoldov1@gmail.com Address: 76 Camp St, Apt 2, Providence RI 02906.

Highlights:

- **Myelin water fraction (MWF) maps could be used to further characterize febrile seizures**
- **All subjects in this study with simple febrile seizures had increased MWF**
- **All subjects in this study with complex febrile seizures had decreased MWF**

Abstract

**Objective*. The objective of this feasibility study was to investigate whether myelin water fraction (MWF) patterns can differentiate children presenting with febrile seizures who will go on to develop nonfebrile epilepsy from those who will not.

Patients and Methods. As part of a prospective study of myelination patterns in pediatric epilepsy, seven subjects with febrile seizures underwent magnetic resonance imaging (MRI) including the following standard sequences—T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR)—and an additional experimental sequence, multicomponent-derived equilibrium single-pulse observation of T1 and T2 (mcDESPOT) to quantify MWF. For each of these subjects, MWF maps were derived and compared with an age-matched population-averaged MWF atlas.

Results. All seven subjects (<5 years old) initially presented with febrile seizures. Of the seven, four had complex seizures and three had simple seizures. All of the children with simple febrile seizures had higher MWF compared with model-derived controls and did not develop epilepsy. All of the children with complex febrile seizures had lower MWF than their model-derived control, and two of these subjects later developed epilepsy.

Conclusion. This is the first study in which MWF maps were used to study children with febrile *seizures. This data suggests that relatively higher or stable MWF compared with normative data indicates a lower risk of nonfebrile epilepsy while relatively lower MWF may indicate a pathological condition that could lead to nonfebrile epilepsy.

Keywords: myelin; epilepsy; febrile; pediatrics

Abbreviations

bSSFP, balanced SSFP

DTI, diffusion tensor imaging

EEG, electroencephalography

FA, fractional anisotropy

FS, febrile seizures

GA, glatiramer acetate

IR-SPGR, inversion recovery SPGR

mcDESPOT, multicomponent-derived equilibrium single-pulse observation of T1 and T2

MRI, magnetic resonance imaging

MWF, myelin water fraction

SPGR, spoiled gradient recalled echo

SSFP, steady-state free precession

PTZ, pentylenetetrazol

1 Introduction

Febrile seizures (FS) are seizure events occurring in children older than 1 month that are associated with a fever not caused by a central nervous system infection (Commission on Epidemiology and Prognosis; International League Against Epilepsy, 1993). They are the most common cause of seizures in children younger than 5 years of age; their peak incidence occurs at 18 months of age (Shinnar, 2003). Because of their association with febrile illnesses, FS are most commonly seen in the winter and the end of summer in correlation with the prevalence of viral upper respiratory illnesses during these time periods (Stokes, Downham, Webb, McQuillin, & Gardner, 1977; Tay, Yip, & Yap, 1983; Verburgh et al., 1992).

Febrile seizures are generally considered benign, and most children experience normal development after seizure events. Unfortunately, there is a small subset of children who experience recurrent FS episodes or go on to develop epilepsy. Prior studies have shown that approximately one third of children with a first-time FS episode will subsequently experience a recurrent event (Hampers & Spina, 2011; Sfaihi et al., 2012; Shinnar & Glauser, 2002). Recurrence appears to be more likely in subjects with a family history of FS, those who present at earlier than 18 months of age, those who present with temperatures <40°C at first convulsion, those with multiple seizures during the same febrile illness, children who attend day nursery, and those who have a seizure within 1 hour of febrile illness onset (Hampers & Spina, 2011; Jones & Jacobsen, 2007; Sfaihi et al., 2012; Shinnar & Glauser, 2002; Waruiru & Appleton, 2004). Children with none of these risk factors have a 4% chance of having further FS, while children with all of these risk factors can have up to 80% chance of further episodes (Fisher et al., 2010; Jones & Jacobsen, 2007; Waruiru & Appleton, 2004). While most children with FS do not

develop epilepsy, a cohor study of 687 children with initial febrile seizures showed a five-fold increased risk of developing unprovoked seizures in these patients compared with control subjects. (Annegers, Hauser, Elveback, & Kurland, 1979; MacDonald, Johnson, Sander, & Shorvon, 1999; Verity, Butler, & Golding, 1985) The risk of developing epilepsy appears to be lower in cases of simple FS (2.4%) and higher in children with febrile seizures with complex features (6-8%). Simple FS is defined as a FS lasting less than 15 minutes and with no focality, while complex FS is defined as one of the following: a seizure lasting longer than 15 minutes, focal manifestations, seizure recurrence in 24 hours, abnormal neurologic examination findings, or history of afebrile seizures in a parent or sibling (Patel et al., 2015; Rosman, 1987). Besides complex FS, other risk factors for progression to epilepsy in children with initial FS include family history of epilepsy, neurodevelopmental impairment, late onset of febrile seizures (>3 years of age), and febrile seizures with a temperature of < 39C (Hwang, Kang, Park, Han, & Kim, 2015; Sapir, Leitner, Harel, & Kramer, 2000; Trinka et al., 2002). Although risk factors for both recurrent FS and epilepsy after FS have been identified, there are no reliable biomarkers available at this time to help clinicians identify which subjects will progress to epilepsy, making it difficult for clinicians to give good counseling to the families (Berg & Shinnar, 1994).

Myelination, which starts as early as the second trimester of gestation, is crucial to the development and maturation of the brain, particularly in the first three years of life (Carmody, Dunn, Boddie-Willis, DeMarco, & Lewis, 2004; Murakami, Weinberger, & Shaw, 1999; van der Knaap et al., 1991). Highlighting its crucial role in development, many major childhood neurologic diseases are related to abnormal myelination, including leukodystrophies, cerebral palsy, and cortical dysplasia (Barkovich, 2000; de Vries, van Haastert, Benders, & Groenendaal,

2011; Fauser et al., 2004; Kolodny, 1993). Therefore, the ability to quantify changes in myelin in children from zero to three years could facilitate our understanding of a wide array of pathological conditions in this age group. One tool for quantitating myelin content is a novel imaging technique called mcDESPOT (multicomponent-derived equilibrium single-pulse observation of T1 and T2). This quantitative magnetic resonance imaging (MRI) technique estimates myelin water fraction (MWF), a surrogate measure of myelin water content, from a series of T1- and T1/T2-weighted images (Deoni, Dean, O'Muircheartaigh, Dirks, & Jerskey, 2012). The mcDESPOT sequence gives us a MWF for each patient that assigns an amount of myelin for every voxel. The values per voxel range from around 0.02 in areas of mostly grey matter and 0.2 to 0.3 for areas of concentrated white matter such as the corpus callosum. We aimed to assess the feasibility of using mcDESPOT imaging to differentiate isolated FS from FS that evolves into epilepsy by comparing individual MWF maps for a group of pediatric subjects with FS with MWF maps of control models of age-matched normally developing children (Dean et al., 2014; Verburgh et al., 1992).

2 Patients and Methods

For this study, subjects with an initial diagnosis of FS for whom there were at least 10 months of follow-up clinical information were included. Patients were selected by first reviewing MRI orders which were placed at Rhode Island Hospital in pediatric patients for seizure work-up, and then the medical record was reviewed to identify subjects with febrile seizures. The initial diagnosis was based on clinical, MRI, and/or electroencephalography (EEG) data. This study is part of a larger prospective study of children with epilepsy; parental consent and subject assent

(when applicable) were obtained in accordance with the Brown Institutional Review Board (protocol #4059-11).

2.1 Magnetic Resonance Imaging

Subjects were scanned at Rhode Island Hospital/Hasbro Children's Hospital using a 1.5T Siemens Espree with an 8-channel head coil or at the Brown University MRI Research Facility with a Siemens 3T Verio with a 12-channel head coil or a Siemens 3T Tim Trio with a 12-channel head coil. Voxel-wise MWF maps were acquired for each participant using mcDESPOT. This technique involves the acquisition of a series of T_1-weighted spoiled gradient recalled echo (SPGR) sequences and T1/T2-weighted balanced steady-state free precession (SSFP) images over a range of flip angles. In addition, an inversion recovery SPGR (IR-SPGR) sequence was acquired to correct for transmit magnetic field inhomogeneities (Deoni, 2011). Whole-brain imaging data were collected with the following parameters: field of view 220 × 220 × 176 mm; image matrix 112 × 112 × 88. Combined, this resulted in approximately 1.8 × 1.8 × 1.8-mm isotropic voxel resolution. Total acquisition time for each subject was less than 12 minutes. The fully detailed description of mcDESPOT parameters is available elsewhere (Deoni et al., 2012).

2.2 Myelin Water Fraction Map Calculation

The post-processing typically involves approximately 24 hours of computer processing. Acquired mcDESPOT images (SPGR, IR-SPGR, and balanced SSFP (bSSFP)) are first linearly coregistered to account for subtle head movement (Jenkinson, Bannister, Brady, & Smith, 2002), and then nonparenchymal voxels are removed (Smith et al., 2004). The MWF map was calculated for each voxel by fitting the SPGR and bSSFP data to a 3-pool tissue model that

estimates fractional volumes and relaxation times for intra- and extra-axonal water, myelin-associated water, and nonexchanging free water (Deoni, Matthews, & Kolind, 2013). Additional corrections were made for radiofrequency flip angle (B_1) and main magnetic field (B_0) inhomogeneities (Deoni, 2010).

MWF maps were aligned to a common analysis space to allow comparisons across subjects and controls. A pediatric T1-weighted template was used as the reference space to which MWF maps of the current study were registered (Deoni et al., 2012). The high flip angle SPGR image and symmetric diffeomorphic normalization were used to determine the transformations needed to map an individual's raw data space to this template space (Avants, Epstein, Grossman, & Gee, 2008). These resulting transformations were applied to each individual's MWF map, aligning each MWF map to the reference template. Full details regarding image normalization are described elsewhere (Deoni et al., 2012).

2.3 Control MWF Construction and Comparison

Control MWF maps were generated for each subject using a predictive growth model shown to characterize patterns of myelination (Dean et al., 2014; Dean et al., 2015) and constructed from a large, longitudinal study examining normative white matter development throughout early childhood (Deoni et al., 2012). Using the subject's age and model parameters previously estimated from the large typically developing cohort, a model-derived MWF map was calculated (Dean et al., 2014). The standard deviation of MWF at each voxel (i.e., standard deviation map, δMWF) was generated (Smith et al., 2004). The model-derived MWF map provides a representative estimate of normative MWF at the specified age, while δMWF provides an

estimate of the variability of MWF at the specified age (Dean et al., 2014). The model-derived MWF and δMWF maps were used to compare subjects' MWFs by calculating a Z-statistic at each voxel using the following formula:

$$Z_{(i,j,k)} = \frac{MWF^{S}_{(i,j,k)} - MWF^{C}_{(i,j,k)}}{\delta MWF_{(i,j,k)}}$$

where $MWF^{S}_{(i,j,k)}$ corresponds to the subjects' MWF at voxel (i,j,k), while $MWF^{C}_{(i,j,k)}$ and $\delta MWF_{(i,j,k)}$ is the model-derived MWF and standard deviation of MWF at voxel (i,j,k). Areas of significant deviation from the model-derived MWF were defined as $|Z| > 2.326$, corresponding to $p < 0.01$.

3 Results

Seven subjects (3 male, 4 female) who initially presented with FS were included in this study (Table 1). Three had simple seizures and four had complex seizures. The average age at time of MRI was 25.6±17.7 months (mean ± standard deviation). The time between first febrile seizure and the performance of the mcDESPOT MRI sequence ranged between 11 days and 17 months for the 7 subjects. The average follow-up time was 32.1±21.3 months; the shortest follow-up was 10 months and the longest follow-up interval was 61 months.

The 3 subjects who had simple FS had higher MWF (defined as individual voxels >2.326) than their model-derived control. The three subjects with higher MWF also had normal MRI scans (no EEG follow-up), and none had epilepsy at follow-up (Figure 1). Four subjects, who all had complex seizures, had lower MWF than their control. Of these, the two with the largest negative difference in MWF developed epilepsy. Subject #3 had the largest negative difference in MWF

of this cohort; this subject also had an abnormal MRI that showed left hippocampal dysplasia, an abnormal EEG that showed generalized epilepsy. This subject developed primary generalized epilepsy (Figure 2). The other subject with a large negative difference in MWF (subject #5) had a normal MRI but an abnormal EEG showing bitemporal spikes. He also developed generalized epilepsy during the follow-up period (Figure 3). The other two subjects with lower MWF (#6 and #7) showed only small negative differences. Subject #6 had a possible left parietal focal cortical dysplasia and an EEG that showed left slowing, and subject #7 had a normal MRI but an EEG showing right slowing (Figure 4). These results are summarized in Table 1.

4 Discussion

This study obtained MWF maps in pediatric subjects presenting with FS to compare their myelination patterns with those of model-derived controls. Of the seven participants, two developed epilepsy, and these subjects had significantly lower MWF when compared with their model-derived controls. Two subjects had slightly lower MWF than the control model, but they did not develop epilepsy. In comparison with those in the subjects who developed epilepsy, these reductions in MWF were observed in fewer areas. All subjects with lower MWFs had complex FS. The three subjects with relatively higher MWF than the model-derived control models had normal MRI scans and simple FS and did not develop epilepsy.

4.1 Current FS Diagnosis

Childhood FSs are considered to be relatively benign but can be a risk factor for the later development of epilepsy. In children with focal, prolonged, or recurrent FSs, the risk of epilepsy later in life can be as high as 57% (Annegers et al., 1979). Other than complex FSs, factors such

as neurodevelopmental abnormalities, family history of epilepsy, and fever duration have been cited as risk factors for developing epilepsy after a FS (Berg et al., 1997).

*In this study, we found that the EEG and MRI scan data did not help predict which children would develop epilepsy. Two of the seven subjects had abnormal MRI scans, but only one of these developed epilepsy. Four of the seven had abnormal EEGs, but only two of these developed epilepsy. Therefore, our results are similar to those from larger studies that show that traditional MRI and EEG are not sensitive or specific enough to predict which patients with FSs will progress to full epilepsy (Nordli et al., 2012; Shinnar et al., 2012).

4.2 Myelin, FSs, and Epilepsy

Animal models and clinical studies have increasingly shown that there is a relationship between damage to the myelin sheath and epilepsy (Hu et al., 2016; Pujar et al., 2017; Widjaja et al., 2013; Yoong et al., 2013). Hu et al. (2016) examined brain tissue from subjects who underwent lesionectomy for intractable epilepsy. The authors found decreased oligodendrocytes and demyelination in epilepsy subjects compared with controls. A rat model that compared rates of myelination between rats bred for enhanced susceptibility to epileptogenesis and rats bred for resistance found that there were relative delays in myelination and neurodevelopment in the seizure-prone rats (Sharma, Powell, Wlodek, O'Brien, & Gilby, 2018). Demyelination has also been observed in the cerebral cortex and hippocampus of the pentylenetetrazol (PTZ)-induced epilepsy rat model (You et al., 2011). To decrease seizures in this rat population, You et al. (2013) used glatiramer acetate (GA), an anti-demyelination drug, to treat the PTZ-induced epileptic rats. They found that the GA-treated animals had significantly fewer epileptiform

discharges and had reduced frequency of seizures compared with controls, suggesting that epilepsy-associated demyelination may be contributing to seizure behavior and that myelin protection can improve symptomatology (You et al., 2011; You et al., 2013).

Currently, the best imaging technique for looking at white matter changes in epilepsy is diffusion tensor imaging (DTI). Focal epilepsy and focal cortical dysplasias have been shown to be associated with decreased white matter and decreased fractional anisotropy (FA) (Shepherd et al., 2013; Slinger, Sinke, Braun, & Otte, 2016). In FSs, DTI has been used to study changes in the white matter tracts at 1 month, 6 months, and 1 year of age and up to 8 years after FS occurrence (Pujar et al., 2017; Widjaja et al., 2013; Yoong et al., 2013). Early DTI analysis in a cohort of FS patients showed decreased FA at 1 and 6 months after FS (Yoong et al., 2013). However, long-term follow-up actually showed overall increases in FA in the caudal and central white matter tracts, suggesting that there is a significant recovery and remyelination process (Pujar et al., 2017). Of note, in the long-term follow-up that showed increased FA, subjects who subsequently developed epilepsy were not included in the analysis (Pujar et al., 2017).

4.3 Myelin Imaging and mcDESPOT

McDESPOT is a quantitative myelin imaging sequence that visualizes MWF throughout the brain. This sequence provides dynamic information about the quantity, organization, and relative amount of myelin. Compared with DTI studies, the mcDESPOT sequence gives us quantitative information that is sensitive to myelin content as well as the ability to compare individual MWF maps with a large model-derived control population (Dean et al., 2015).

*In this analysis of 7 patients who initially presented with FS, conventional MRI scans and EEGs did not provide much differentiation within the group. The conventional MRI scans for these patients showed very subtle, if any, changes. One patient had a subtle left hippocampal dysplasia and another had a possible left parietal focal cortical dysplasia. However, when the MWF maps were analyzed, the 3 patients with simple FSs showed higher MWF and the 4 patients with complex FS had lower MWF compared with the model-derived controls. Therefore, the MWF maps that show myelination relative to the model-derived control have the potential to show more differentiation and pathology than conventional imaging.

Of the patients with lower MWF, one (subject #3, Figure 2) showed significant differences throughout all major white matter tracts. This patient subsequently progressed to generalized epilepsy. Subject 5 also had lower MWF (Figure 3) and developed epilepsy, but the differences were in a more peripheral but still statistically significant pattern. Two other subjects (#6 and #7, Figure 4) showed some scattered areas of lower MWF but they did not develop epilepsy. These patterns of significantly lower MWF in the subjects who developed epilepsy are consistent with animal models showing epilepsy-associated demyelination and clinical studies of focal epilepsy and focal cortical dysplasias showing areas of decreased myelination compared with the control model (Shepherd et al., 2013; Slinger et al., 2016). Therefore, this finding adds to the body of evidence seen in human diffusion imaging and animal models that there is a relationship between white matter decreases and epilepsy.

Of further significance were the markedly higher (relative to the control model) MWF in subjects who did not develop epilepsy (subjects #1, #2, and #4, Figure 1). Higher levels of myelination

have been observed previously in the long-term follow-up of patients with FS who did not develop epilepsy (Pujar et al., 2017). More specifically, patients with prolonged FS showed initial decreases in FA values at one and six months then had FA increases at 8-year follow-up. More specifically, at the 8-year follow-up, there was increased FA in central white matter tracts, increased mean and axial diffusivity in peripheral white matter tracts and late maturing central white matter tracts, and increased radial diffusivity in peripheral white matter tracts (Pujar et al., 2017). It is important to note, however, that FA values are not the same as MWF values. If fibers increase in coherence, FA values will increase regardless of actual myelin content.

In our cohort, MRI scans were performed within a month of FS occurrence, and 3 patients had higher MWF compared with the model-derived control. None of these patients developed epilepsy. This increased MWF could indicate that there is more myelin in these patients compared with controls or that increased myelin could also be in a more disorganized pattern, which is represented as decreased FA values in DTI analysis. We did not perform a DTI analysis on all patients and therefore cannot make any conclusions about the coherence of the myelin. It is possible that increased MWF could be an indicator of a more robust myelin repair process that could protect against the development of full epilepsy, as decreased myelination has been shown to be associated with epilepsy (Shepherd et al., 2013; Slinger et al., 2016).

4.4 Limitations

This was a small feasibility study of seven patients. The follow-up period was also limited, and it is unknown if any additional children will progress to epilepsy. Therefore, we only report our

observations that the mcDESPOT sequence should be further investigated as a potential tool for assessing the structural and functional changes that may be correlated with FS prognosis.

5 Conclusions

*These results support the hypothesis that for children presenting with FS, lower MWF in comparison with a model-derived control may portend a higher risk of developing epilepsy later in life and higher MWF in comparison with a model-derived control may indicate a lower risk of development of epilepsy and simple FS.

Acknowledgments

The authors would like to thank Sue Foley and Wendy Smith of the Rhode Island Hospital Department of Diagnostic Imaging for all of their invaluable support in recruiting subjects and Kristin Kraus for her editorial assistance.

List of Funding Sources

This work was supported by the National Institute of Mental Health (award R01 MH087510) and the Bill & Melinda Gates Foundation, Seattle, WA. S.C.L.D. receives continuing support from the Bill & Melinda Gates Foundation. D.C.D. is supported by the National Institutes of Mental Health (award K99MH110596) and in part by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (award U54 HD090256 to the Waisman Center). J.O.M. is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (grant number 206675/Z/17/Z).

References

Annegers, J. F., Hauser, W. A., Elveback, L. R., & Kurland, L. T. (1979). The risk of epilepsy following febrile convulsions. *Neurology, 29*(3), 297-303.

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal, 12*(1), 26-41. doi:10.1016/j.media.2007.06.004

Barkovich, A. J. (2000). Concepts of myelin and myelination in neuroradiology. *AJNR Am J Neuroradiol, 21*(6), 1099-1109.

Berg, A. T., & Shinnar, S. (1994). The contributions of epidemiology to the understanding of childhood seizures and epilepsy. *J Child Neurol, 9 Suppl 2*, 19-26.

Berg, A. T., Shinnar, S., Darefsky, A. S., Holford, T. R., Shapiro, E. D., Salomon, M. E., . . . Hauser, A. W. (1997). Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med, 151*(4), 371-378.

Carmody, D. P., Dunn, S. M., Boddie-Willis, A. S., DeMarco, J. K., & Lewis, M. (2004). A quantitative measure of myelination development in infants, using MR images. *Neuroradiology, 46*(9), 781-786. doi:10.1007/s00234-004-1241-z

Commission on Epidemiology and Prognosis; International League Against Epilepsy. (1993). Guidelines for epidemiologic studies on epilepsy. *Epilepsia, 34*(4), 592-596.

de Vries, L. S., van Haastert, I. C., Benders, M. J., & Groenendaal, F. (2011). Myth: cerebral palsy cannot be predicted by neonatal brain imaging. *Semin Fetal Neonatal Med, 16*(5), 279-287. doi:10.1016/j.siny.2011.04.004

Dean, D. C., 3rd, O'Muircheartaigh, J., Dirks, H., Waskiewicz, N., Lehman, K., Walker, L., . . . Deoni, S. C. (2014). Modeling healthy male white matter and myelin development: 3 through 60months of age. *Neuroimage, 84*, 742-752. doi:10.1016/j.neuroimage.2013.09.058

Dean, D. C., 3rd, O'Muircheartaigh, J., Dirks, H., Waskiewicz, N., Walker, L., Doernberg, E., . . . Deoni, S. C. (2015). Characterizing longitudinal white matter development during early childhood. *Brain Struct Funct, 220*(4), 1921-1933. doi:10.1007/s00429-014-0763-3

Deoni, S. C. (2010). Quantitative relaxometry of the brain. *Top Magn Reson Imaging, 21*(2), 101-113. doi:10.1097/RMR.0b013e31821e56d8

Deoni, S. C. (2011). Correction of main and transmit magnetic field (B0 and B1) inhomogeneity effects in multicomponent-driven equilibrium single-pulse observation of T1 and T2. *Magn Reson Med, 65*(4), 1021-1035. doi:10.1002/mrm.22685

Deoni, S. C., Dean, D. C., 3rd, O'Muircheartaigh, J., Dirks, H., & Jerskey, B. A. (2012). Investigating white matter development in infancy and early childhood using myelin water faction and relaxation time mapping. *Neuroimage, 63*(3), 1038-1053. doi:10.1016/j.neuroimage.2012.07.037

Deoni, S. C., Matthews, L., & Kolind, S. H. (2013). One component? Two components? Three? The effect of including a nonexchanging "free" water component in multicomponent driven equilibrium single pulse observation of T1 and T2. *Magn Reson Med, 70*(1), 147-154. doi:10.1002/mrm.24429

Fauser, S., Schulze-Bonhage, A., Honegger, J., Carmona, H., Huppertz, H. J., Pantazis, G., . . . Zentner, J. (2004). Focal cortical dysplasias: surgical outcome in 67 patients in relation to

histological subtypes and dual pathology. *Brain, 127*(Pt 11), 2406-2418. doi:10.1093/brain/awh277

Fisher, C. G., DiPaola, C. P., Ryken, T. C., Bilsky, M. H., Shaffrey, C. I., Berven, S. H., . . . Fourney, D. R. (2010). A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine (Phila Pa 1976), 35*(22), E1221-1229. doi:10.1097/BRS.0b013e3181e16ae2

Hampers, L. C., & Spina, L. A. (2011). Evaluation and management of pediatric febrile seizures in the emergency department. *Emerg Med Clin North Am, 29*(1), 83-93. doi:10.1016/j.emc.2010.08.008

Hu, X., Wang, J., Gu, R., Qu, H., Li, M., Chen, L., . . . Yuan, P. (2016). The relationship between the occurrence of intractable epilepsy with glial cells and myelin sheath–an experimental study. *Eur Rev Med Pharmacol Sci, 20*(21), 4516-4524.

Hwang, G., Kang, H. S., Park, S. Y., Han, K. H., & Kim, S. H. (2015). Predictors of unprovoked seizure after febrile seizure: short-term outcomes. *Brain Dev, 37*(3), 315-321. doi:10.1016/j.braindev.2014.06.003

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.

Jones, T., & Jacobsen, S. J. (2007). Childhood febrile seizures: overview and implications. *Int J Med Sci, 4*(2), 110-114.

Kolodny, E. H. (1993). Dysmyelinating and demyelinating conditions in infancy. *Curr Opin Neurol Neurosurg, 6*(3), 379-386.

MacDonald, B. K., Johnson, A. L., Sander, J. W., & Shorvon, S. D. (1999). Febrile convulsions in 220 children--neurological sequelae at 12 years follow-up. *Eur Neurol, 41*(4), 179-186. doi:10.1159/000008048

Murakami, J. W., Weinberger, E., & Shaw, D. W. (1999). Normal myelination of the pediatric brain imaged with fluid-attenuated inversion-recovery (FLAIR) MR imaging. *AJNR Am J Neuroradiol, 20*(8), 1406-1411.

Nordli, D. R., Jr., Moshe, S. L., Shinnar, S., Hesdorffer, D. C., Sogawa, Y., Pellock, J. M., . . . Sun, S. (2012). Acute EEG findings in children with febrile status epilepticus: results of the FEBSTAT study. *Neurology, 79*(22), 2180-2186. doi:10.1212/WNL.0b013e3182759766

Patel, N., Ram, D., Swiderska, N., Mewasingh, L. D., Newton, R. W., & Offringa, M. (2015). Febrile seizures. *BMJ, 351*, h4240.

Pujar, S. S., Seunarine, K. K., Martinos, M. M., Neville, B. G. R., Scott, R. C., Chin, R. F. M., & Clark, C. A. (2017). Long-term white matter tract reorganization following prolonged febrile seizures. *Epilepsia, 58*(5), 772-780. doi:10.1111/epi.13724

Rosman, N. P. (1987). Febrile seizures. *Emerg Med Clin North Am, 5*(4), 719-737.

Sapir, D., Leitner, Y., Harel, S., & Kramer, U. (2000). Unprovoked seizures after complex febrile convulsions. *Brain Dev, 22*(8), 484-486.

Sfaihi, L., Maaloul, I., Kmiha, S., Aloulou, H., Chabchoub, I., Kamoun, T., & Hachicha, M. (2012). Febrile seizures: an epidemiological and outcome study of 482 cases. *Childs Nerv Syst, 28*(10), 1779-1784. doi:10.1007/s00381-012-1789-6

Sharma, P., Powell, K. L., Wlodek, M. E., O'Brien, T. J., & Gilby, K. L. (2018). Delayed myelination and neurodevelopment in male seizure-prone versus seizure-resistant rats. *Epilepsia*. doi:10.1111/epi.14013

Shepherd, C., Liu, J., Goc, J., Martinian, L., Jacques, T. S., Sisodiya, S. M., & Thom, M. (2013). A quantitative study of white matter hypomyelination and oligodendroglial maturation in focal cortical dysplasia type II. *Epilepsia, 54*(5), 898-908. doi:10.1111/epi.12143

Shinnar, S. (2003). Febrile Seizures and Mesial Temporal Sclerosis. *Epilepsy Curr, 3*(4), 115-118. doi:10.1046/j.1535-7597.2003.03401.x

Shinnar, S., Bello, J. A., Chan, S., Hesdorffer, D. C., Lewis, D. V., Macfall, J., . . . Team, F. S. (2012). MRI abnormalities following febrile status epilepticus in children: the FEBSTAT study. *Neurology, 79*(9), 871-877. doi:10.1212/WNL.0b013e318266fcc5

Shinnar, S., & Glauser, T. A. (2002). Febrile seizures. *J Child Neurol, 17 Suppl 1*, S44-52. doi:10.1177/08830738020170010601

Slinger, G., Sinke, M. R., Braun, K. P., & Otte, W. M. (2016). White matter abnormalities at a regional and voxel level in focal and generalized epilepsy: A systematic review and meta-analysis. *Neuroimage Clin, 12*, 902-909. doi:10.1016/j.nicl.2016.10.025

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Suppl 1*, S208-219. doi:10.1016/j.neuroimage.2004.07.051

Stokes, M. J., Downham, M. A., Webb, J. K., McQuillin, J., & Gardner, P. S. (1977). Viruses and febrile convulsions. *Arch Dis Child, 52*(2), 129-133.

Tay, J. S., Yip, W. C., & Yap, H. K. (1983). Seasonal variations in admissions to a tropical paediatric unit. *Trop Geogr Med, 35*(2), 167-172.

Trinka, E., Unterrainer, J., Haberlandt, E., Luef, G., Unterberger, I., Niedermüller, U., . . . Bauer, G. (2002). Childhood febrile convulsions--which factors determine the subsequent epilepsy syndrome? A retrospective study. *Epilepsy Res, 50*(3), 283-292.

van der Knaap, M. S., Valk, J., Bakker, C. J., Schooneveld, M., Faber, J. A., Willemse, J., & Gooskens, R. H. (1991). Myelination as an expression of the functional maturity of the brain. *Dev Med Child Neurol, 33*(10), 849-857.

Verburgh, M. E., Bruijnzeels, M. A., van der Wouden, J. C., van Suijlekom-Smit, L. W., van der Velden, J., Hoes, A. W., & Offringa, M. (1992). Incidence of febrile seizures in The Netherlands. *Neuroepidemiology, 11*(4-6), 169-172.

Verity, C. M., Butler, N. R., & Golding, J. (1985). Febrile convulsions in a national cohort followed up from birth. II--Medical history and intellectual ability at 5 years of age. *Br Med J (Clin Res Ed), 290*(6478), 1311-1315.

Waruiru, C., & Appleton, R. (2004). Febrile seizures: an update. *Arch Dis Child, 89*(8), 751-756. doi:10.1136/adc.2003.028449

Widjaja, E., Kis, A., Go, C., Raybaud, C., Snead, O. C., & Smith, M. L. (2013). Abnormal white matter on diffusion tensor imaging in children with new-onset seizures. *Epilepsy Res, 104*(1-2), 105-111. doi:10.1016/j.eplepsyres.2012.10.007

Yoong, M., Seunarine, K., Martinos, M., Chin, R. F., Clark, C. A., & Scott, R. C. (2013). Prolonged febrile seizures cause reversible reductions in white matter integrity. *Neuroimage Clin, 3*, 515-521. doi:10.1016/j.nicl.2013.10.010

You, Y., Bai, H., Wang, C., Chen, L. W., Liu, B., Zhang, H., & Gao, G. D. (2011). Myelin damage of hippocampus and cerebral cortex in rat pentylenetetrazol model. *Brain Res, 1381*, 208-216. doi:10.1016/j.brainres.2011.01.011

You, Y., Zhao, Y., Bai, H., Liu, Z., Meng, F., Zhang, H., & Xu, R. (2013). Glatiramer acetate, an anti-demyelination drug, reduced rats' epileptic seizures induced by pentylenetetrazol via protection of myelin sheath. *Eur J Pharm Sci, 49*(3), 366-370. doi:10.1016/j.ejps.2013.04.014

Table 1: Study patient characteristics and results

Subject	Patient age	Patient sex	Seizure Type	MWF (p<0.05)*	MRI	EEG	Time from FS to MRI	F/U Length (months)	Epilepsy
1	11 mo	M	S	Increased	Normal	None	21d	61	N
2	2 yr	F	S	Increased	Normal	None	16d	24	N
3	3 yr	M	C	Decreased	Abnormal†	Abnormal	17mo	13	Y
4	5 yr	F	S	Increased	Normal	None	11d	55	N
5	1 yr	M	C	Decreased	Normal	Abnormal	43d	46	Y
6	2 yr	F	C	Decreased	Abnormal^	Abnormal	11d	16	N
7	1 yr	F	C	Decreased	Normal	Abnormal	28d	10	N

F/U = follow-up; S = simple; C = complex

*****MWF is reported as higher or lower when compared to an age-matched control.

†Left hippocampal dysplasia

^ Possible left parietal focal cortical dysplasia

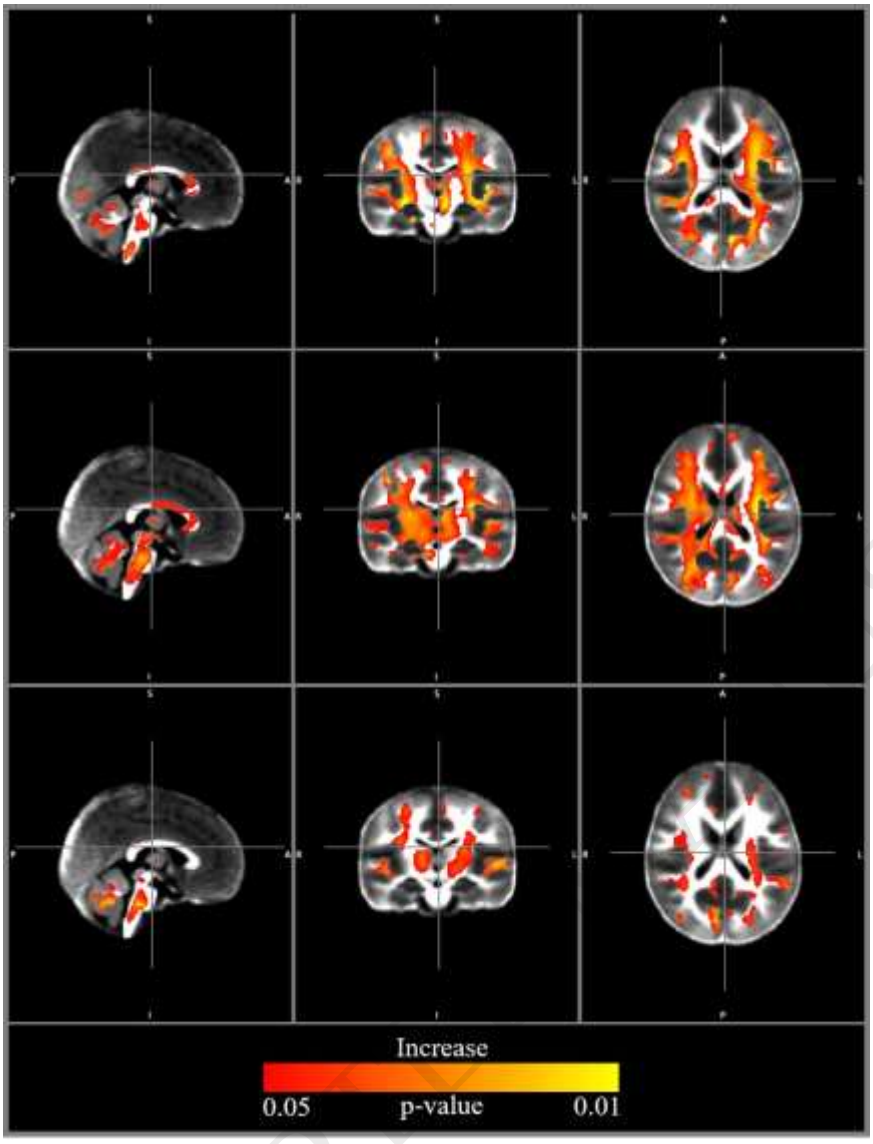

Figure 1. Sagittal (left), coronal (center), and axial (right) MWF maps in subjects #1 (top), #2 (middle), and #4 (bottom) showing areas of higher MWF (in red) compared with control model ($P<0.05$). These subjects had normal MRI scans and did not progress to epilepsy.

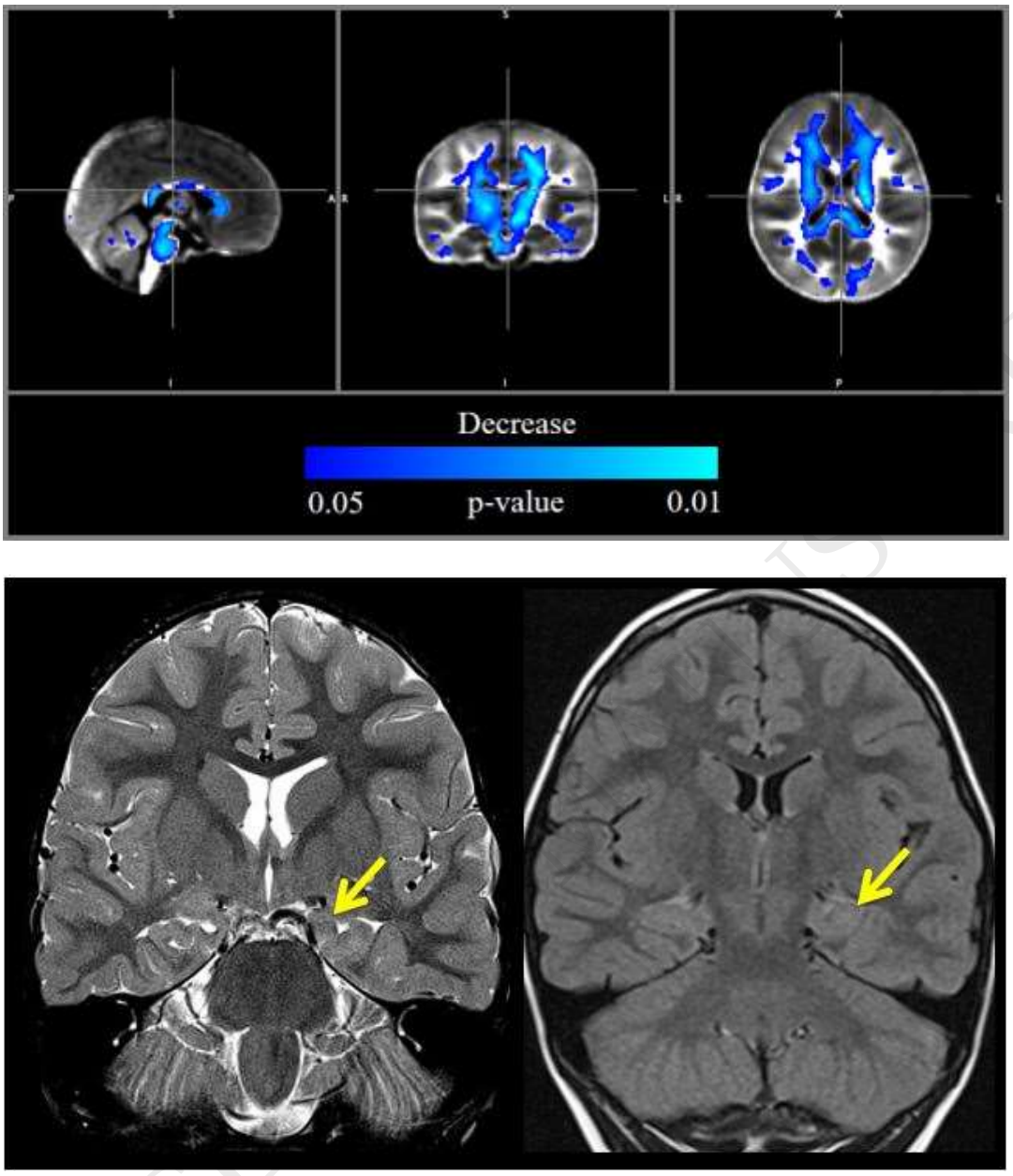

Figure 2. (Top) Sagittal (left), coronal (center), and axial (right) MWF maps of subject #3 showing areas of lower MWF (in blue) compared with control model ($P<0.05$). This subject progressed to develop primary generalized epilepsy. (Bottom) T2-weighted and FLAIR MRI images of subject #3 showing mild left hippocampal dysplasia with a foreshortened left hippocampus and vertically oriented parahippocampal gyru (arrows show the mild hippocampal dysplasia).

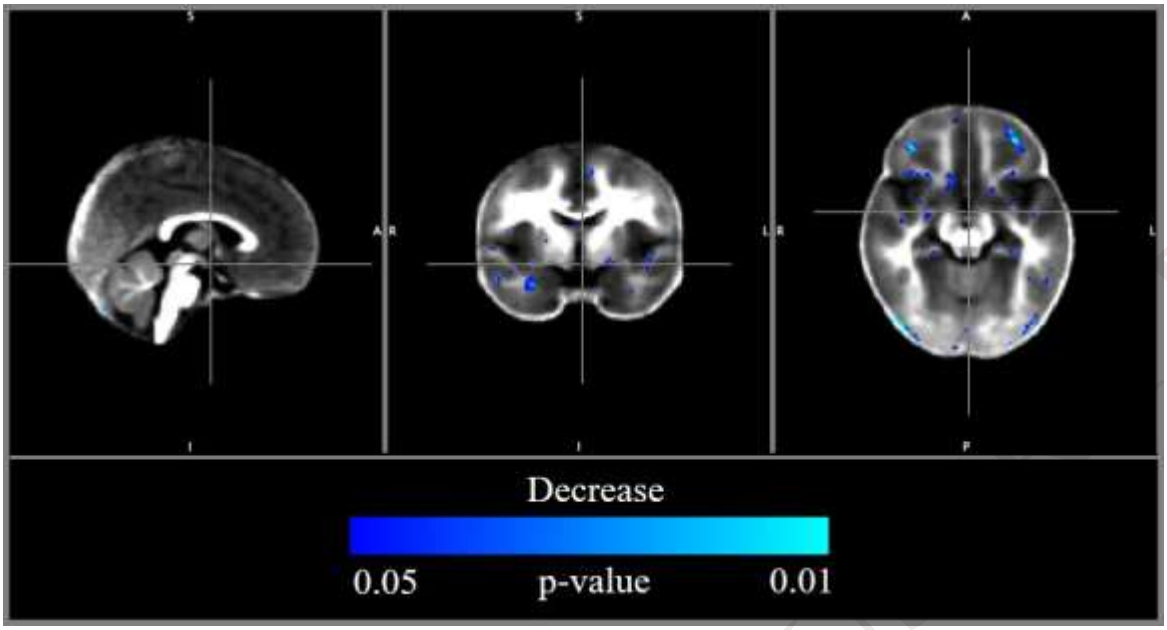

Figure 3. Sagittal (left), coronal (center), and axial (right) MWF maps of subject #5 showing areas of lower MWF (in blue) compared with control model ($P<0.05$). The subject progressed to develop epilepsy.

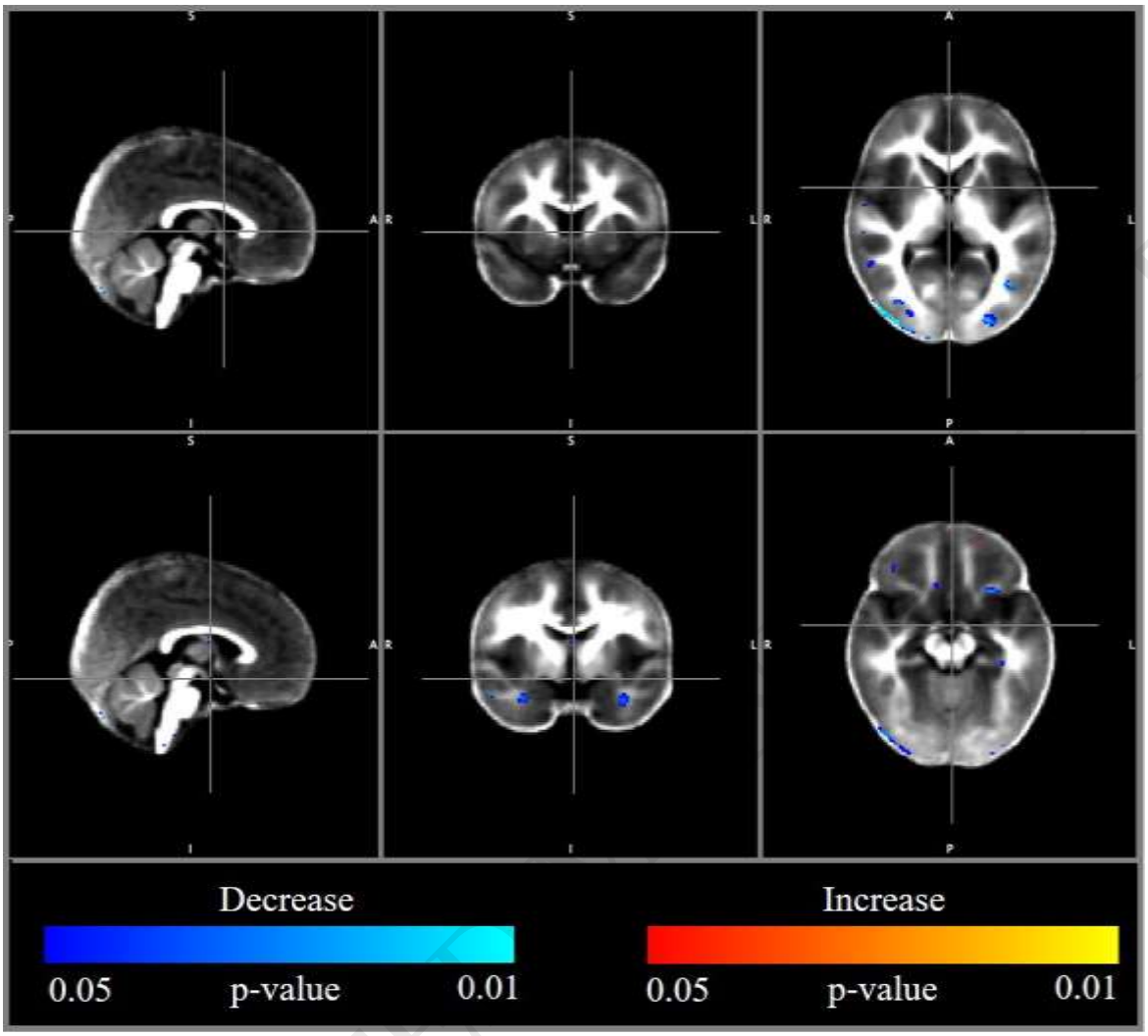

Figure 4. Sagittal (left), coronal (center), and axial (right) MWF maps of subjects #6 (top) and #7 (bottom) showing scattered areas of decreased MWF (in blue) compared with control model ($P<0.05$). These two subjects did not progress to epilepsy.